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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/687,911	10/13/2000	Rostyslav Stoika	CEDAR-44649	9562

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EXAMINER	
LI, QIAN J	

ART UNIT	PAPER NUMBER
1632	13

DATE MAILED: 01/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/687,911	STOIKA ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35 and 53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35, 53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6,9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election of Group V, claims 35 and 53, in Paper No. 12 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-34 and 36-52 have been canceled. Election was made **without** traverse in Paper No. 12.

Claims 35 and 53 are pending and under current examination.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 119 and 120 as follows:

> The second application must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the second application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ 2d 1077 (Fed. Cir. 1994).

This application claims benefit of priority to U.S. application 60/031,338, 08/894.251, PCT/US97/21463, and 09/569,956. However, the association of PTTG with T lymphocytes, and the changes of PTTG mRNA in response to immunosuppressive agents were not disclosed in the cited applications. Therefore, the priority date of the instant application has been established as the filing date of the instant application, i.e. 10/13/2000. Applicant is invited to submit evidence pointing to the serial number, page and line where support can be found establishing an earlier priority date.

Specification

The disclosure is objected to because of the following informalities: The brief description of the drawings lacks complete information regarding the items in the drawing. For example, figures 9-13 have multiple columns for each group in the figure, however, it is unclear what each column represents, e.g. a different type of cell or a duplication of the same type of cell.

Appropriate correction is required.

Claim Objections

Claim 35 is objected to because of the claim recitation, "PTTG". The term should be spelled out the first time it appears in the claims.

Claims 35 and 53 are objected to because a conjunction word is missing before the last phrase of the claims.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 35 and 53 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as

to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the nature of the claims relative to the state of the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention without undue experimentation.

The claims are drawn to an *in vitro* method for screening new immunosuppressive or immunoenhancing agents comprising exposing cultured T-lymphocytes to a potential immunosuppressive agent or an immunoenhancing agent, and detecting a change in the expression level of PTTG in the T-lymphocytes compared to control lymphocytes, wherein dowregulation of PTTG expression being indicative of an immunosuppressive capacity, and upregulation of PTTG expression being indicative of an immunoenhancing capacity.

The specification teaches that PTTG mRNA and protein expressions are cell cycle-dependent and peak at G2/M phase, that PTTG mRNA expression could be detected in many different tumor cells (table 16), that when resting human T cells were

treated with a T-cell mitogen, e.g. anti-CD3 antibody, T cells began to proliferate and sequentially entered S phase and G2/M phase. Parallel to this proliferation is the PTTG mRNA expression, which was dramatically increased for more than 30 times from the levels in the resting T cells (fig. 5). When the activated T cells were treated with various agents, such as immunosuppressive hydrocortisone, cyclosporine A (CPA), and TGF-β1, or antibiotics aphidicolin, or antineoplastics nocodazole, the expression of PTTG mRNA was suppressed to various degree, with the cyclosporine A being the most effective. However, the experimentation was conducted only in T cells, normal or leukemic. Therefore, when the data were considered with what is known in the art, a doubt is raised on whether the changes of PTTG mRNA level in T cells in response to various agents are immunological related or cell cycle related.

For example, *Ramos-Morales et al* (Oncogene 2000 Jan;19:403-409) teach, "HUMAN PTTG IS EXPRESSED AT HIGH LEVELS IN TESTIS AND THYMUS, ORGANS WHERE THERE ARE MANY ACTIVELY PROLIFERATING CELLS", "IN ADDITION, THE EXPRESSION WAS ELEVATED IN JURKAT (A LYMPHOMA T CELL LINE) AS WELL AS IN PRIMARY HEMATOPOIETIC TUMORS. EXAMINATION OF SEVERAL DIFFERENT TUMOR CELL LINES BY NORTHERN BLOT INDICATES THAT THESE LINES ALL CONTAIN HIGH LEVELS OF HPTTG MRNA. THESE DATA SUGGEST THAT HPTTG IS PREFERENTIALLY EXPRESSED IN PROLIFERATING CELLS" (right column, page 404) *Zhang et al* (Mol Endo 1999 Feb;13:156-166, IDS/30) teach the tissue distribution of hpttg, "A STRONG MRNA SIGNAL OF APPROXIMATELY 0.8 KB WAS DETECTED IN HUMAN FETAL LIVER. IN NORMAL HUMAN ADULT TISSUES, ABUNDANT PTTG EXPRESSION WAS EVIDENT IN TESTIS. STRONG EXPRESSION WAS ALSO OBSERVED IN THYMUS, AND WEAK EXPRESSION SIGNALS WERE SEEN IN COLON, SMALL INTESTINE, BRAIN, PLACENTA, AND PANCREAS. INTERESTINGLY, WHEN HUMAN MALIGNANT TUMOR CELLS WERE

TESTED, PTTG WAS FOUND TO BE HIGHLY EXPRESSED IN ALL CELL LINES EXAMINED" (left column, page 159). Apparently, the expression of hpttg mRNA expression is not limited to immune cells or organs, rather, is closely related to the proliferating state of the cells. *Ramos-Morales et al* clearly teaches, in the Discussion section of the cited art, "THAT HPTTG PROTEIN LEVELS ARE UP-REGULATED IN RAPIDLY GROWING CELLS, AND DOWN-REGULATED IN CONFLUENT AND SERUM-STARVED CELLS, AND ARE EXPRESSED AT HIGHEST LEVELS IN SYNCHRONIZED CELLS IN THE M PHASE CONFIRM OUR HYPOTHESIS THAT THE EXPRESSION OF THIS PROTO-ONCOGENE RESPONDS TO CHANGES IN GROWTH CONDITIONS", "OUR RESULTS PREDICT THAT ANY STIMULUS OR GENETIC ALTERATION LEADING TO CELL PROLIFERATION WOULD LEAD TO HIGH STEADY-STATE HPTTG LEVEL" (page 407). In the instant case, the immunosuppressants, particularly the CPA and TGF-β, are known immune suppressive agents as well as cell cycle regulators. *Janeway et al* (Immunobiology, 5th edition, New York and London: Garland Publishing; c2001.) teach that corticosteroids are powerful anti-inflammatory drugs that alter the transcription of as many as 1% of genes in the genome (§ 14-1); that CPA is cyclic decapeptide and interferes with T-cell signaling. MeSH describes TGF-β as inducing phenotypic transformation and has a potential role in embryonic development, cellular differentiation, hormone secretion, and immune function. Accordingly, by changing the gene expression and proliferation state of T cells, these agents could influence the levels of hpttg expression. In view the foregoing teachings, the T cell response observed by the applicants could be interpreted as a response to a stimulus or gene alteration leading to the change in cell proliferation state, and subsequently, the changes in PTTG expression. The specification fails to teach the suppressive effect of CPA or hydrocortisone is specific for immune suppression but not

cell cycle suppression, thus, fails to provide sufficient guidance commensurate with the scope of the claims. The selected substance may not necessarily be an immune suppressant or enhancer, but rather a cell cycle regulator (cell cycle suppressor or enhancer). In view of such, the invention does not appear to be enabled in the absence of evidence to the contrary.

Claims are drawn to a method using mammalian T lymphocytes, which T cells encompass normal T lymphocytes, resting and activated T lymphocytes, and T lymphocytes derived from lymphoma or leukemia. However, the specification teaches that hydrocortisone did not inhibit PTTG expression in Jurkat leukemia T cell line, and TGF-β1 did not affect PTTG expression in normal T cells (Specification, page 82, line 13-16, and page 83, lines 22-26). Further, claim 53 does not limit the state of T lymphocytes, however, apparently the resting state of the T lymphocytes would not reflect the changes of PTTG, and exposing T lymphocytes to a potential immunoenhancing agent may not change the proliferative state of the T cells unless the agent is a cell cycle regulator. In view of such, the claims do not appear to be enabled commensurate to the scope of the claims.

Claims are drawn to detecting a change in the expression level of PTTG protein. However, in the working examples of the specification, the changes were detected and demonstrated by its mRNA expression, since such mRNA changes may not necessarily reflected in the expression of the PTTG protein, the specification fails to provide sufficient guidance with regard whether the changes could be detected at the protein

level, the expression patterns of PTTG protein in response to the recited agents, the sensitivities of detection methods, thus, fails to support the full scope of the claims.

Therefore, in view of state of the art relative to the nature and scope of the claims, and the limited guidance of the specification, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 35 and 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are vague and indefinite because the methods comprising a step of detecting a change in the expression level of PTTG in the T-lymphocytes, however, it does not recite a positive step that clearly defines the means for detection, thus, the metes and bounds of the claims are unclear. Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter that claims encompass as well as make clear the subject matter from which others would be precluded, *Ex parte Erlich*, 3 USPQ2d 1011 at 6.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Q. Janice Li whose telephone number is 703-308-7942. The examiner can normally be reached on 8:30 am - 5 p.m., Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah J. Reynolds can be reached on 703-305-4051. The fax numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of formal matters can be directed to the patent analyst, Dianiece Jacobs, whose telephone number is (703) 305-3388.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235. The faxing of such papers must conform to the notice published in the Official Gazette 1096 OG 30 (November 15, 1989).

Q. Janice Li
Examiner
Art Unit 1632

QJL
January 9, 2003

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER